REMARKS

Reconsideration of the above-identified patent application in view of the amendment above and the remarks below is respectfully requested.

Claims 10, 17, 25 and 28-29 have been canceled in this paper. Claims 2-3, 5-7, 9, 11, 16, 18 and 26-27 have been amended in this paper. New claim 30 has been added in this paper. Therefore, claims 1-9, 11-16, 18-24, 26-27 and 30 are pending and are under active consideration.

Claim 10 stands provisionally objected to "as being a substantial duplicate" of claim 9. In view of the cancellation herein of claim 10, the subject objection has been rendered moot and, therefore, should be withdrawn.

Claims 2-3[1], 6-7, 9-17, 25 and 28 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claim 2 is indefinite over the recitation "used and indicated" because it is not clear what the positions are being "used" for as claim 1 does not recite the "use" or "indication" of particular positions. Applicant is advised to use claim language that is consistent with that of claim 1.
>
> In claim [3], the recitation "the reagent for selective conversion of cytosine to uracil" lacks proper antecedent basis because claim 1, while reciting a reagent, does not recite a reagent "for selective conversion of cytosine to uracil."
>
> Claims 6 and 7 are indefinite because they refer to "the genomic DNA," but it is not clear to which genomic DNA they are

[1] Although claim 4, not claim 3, is included in the statement of the rejection, the allegedly indefinite language is found in claim 3, not claim 4. Therefore, it is believed that the identification of claim 4, instead of claim 3, is a typographical error.

intended to refer because claim 1 recites a sample genomic DNA and a reference genomic DNA so it is not clear which is "the" genomic DNA. Claims 9 and 10 are also indefinite over this recitation as they depend from claim 6.

Claim 7 is indefinite over the recitation "in step d) by formation of heteroduplexes with a completely methylated reference DNA," because step (d) does not require a completely unmethylated reference DNA, only a reference genomic DNA, and so if applicant is intending to require here that step (c) of claim 1 must use a unmethylated DNA or if somehow between step (c) and (d) the DNA is unmethylated, etc.

In claim 11, the phrase "the location and/or presence of cleaved...positions" lacks proper antecedent basis in the claim because the claims do not previously recite a cleaved position, therefore it is confusing which cleaved position applicant is referencing. Claims 12-17 are also indefinite over this recitation because they depend from claim 11.

Claim 17 is indefinite because it is not clear what it means to position PCR primers "newly stepwise by the maximally detectable range." It is not clear how primers are positioned by a range of a mass spec, etc. Clarification is required.

Claim 25 is confusing. It is not clear how this claim is meant to further limit claim 1. It is not clear if the claim intends for each of steps (a) to (f) to be repeated in view of the "such that" clause that only recites the repetition of steps (a)-(c). Further the claim requires that a genomic DNA of step (c) is treated according to steps (a) and (b), but claim 1 already appears to require such a step, as step (c) of claim 1 requires that steps (a) and (b) are performed on a reference genomic DNA. Finally, it is not clear what is meant by "the genomic DNA of (a) is treated according to step (c)." It is not clear if applicant is intending to set forth that the "sample" genomic DNA of step (a) is the same as the "reference" genomic DNA of step (c) or some other limitation. The recitations of claim 25 appear to merely restate steps that are already present in claim 1.

Claim 28 is indefinite over the recitation "as different as possible" because it is not clear what this modifies, for example, the DNA, the individuals, the cells, the cell lines, etc. Furthermore, it is

> not clear what "as different as possible" means in this claim, as different as possible with regard to what feature/features?

Insofar as the present rejection pertains to claims 10, 17, 25 and 28, the rejection is moot in view of Applicant's cancellation herein of claims 10, 17, 25 and 28. Insofar as the present rejection pertains to claims 2-3, 6-7, 9 and 11-16, Applicant respectfully traverses the rejection.

With respect to claim 2, the phrase "used and indicated" is no longer recited.

With respect to claim 3, the phrase "the reagent for selective conversion of cytosine to uracil" is no longer recited.

With respect to claims 6 and 7, the type of genomic DNA contemplated is now specifically recited.

With respect to claim 7, the phrase "in step d) by formation of heteroduplexes with a completely methylated reference DNA" is no longer recited.

With respect to claim 11, the dependency of the claim has been changed to new claim 30, which provides antecedent basis for a cleaved position.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claims 16, 18, 26 and 27 stand rejected under 35 U.S.C. 112, first paragraph, "as failing to comply with the written description requirement." In support of the rejection, the Patent Office states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

> In claim 16, the new limitation that primers are "sequential, staggered, consecutive, or overlapping to other PCR primers" appears to be new matter. The specification discusses a series of PCR reactions using primers "set stepwise" (third paragraph page 9) but does not appear to provide basis for sequential, staggered, consecutive, or overlapping PCR primers. The specification does not clearly define what is meant by "set stepwise" and thus this phrase does not appear to provide basis for the newly added limitation.
>
> In claim 18, the new limitation of "that enables the polymerase reaction to be immobilized" in claim 18 appears to represent new matter. While claim 18 provides basis for a primer that would enable a PCR product to be immobilized on a surface, there does not appear to be any support for a method that enables the polymerase reaction itself to be immobilized on a solid support.
>
> In claims 26 and 27 the requirement in part (b) of both claims that "one primer of the polymerase reaction is fluorescently labeled and provided with a chemical function thereby enabling the immobilization of the amplificate on a surface" appears to be new matter. The specification does not appear to provide for such primers. The specification discusses labeled products and processes that can be immobilized, but does not discuss primers modified as required by claims 26 and 27 herein.

Applicant respectfully traverses the present rejection.

With respect to claim 16, Applicant has replaced the phrase "sequential, staggered, consecutive, or overlapping" with the phrase "set stepwise." Applicant notes that the Patent Office acknowledges in the present rejection that the present specification provides support for the "set stepwise" language. In reply to the Patent Office's contention that "set stepwise" is not defined in the present specification, Applicant respectfully submits that one of ordinary skill in the art would understand the meaning of this language.

With respect to claim 18, Applicant notes that the Patent Office acknowledges in the present rejection that the present specification provides support for a primer that would enable a PCR product to be immobilized on the surface. Claim 18 has been amended accordingly.

With respect to claims 26 and 27, Applicant notes that the Patent Office acknowledges in the present rejection that the present specification provides support for labeled products that can be immobilized. Claims 26 and 27 have been amended accordingly.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claims 6, 9 and 10 stand rejected under 35 U.S.C. 112, first paragraph, "as failing to comply with the enablement requirement." In support of the rejection, the Patent Office states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention.
>
> Claim 6 is drawn to a method for detecting the presence of 5-methylcytosine positions in a sample genomic DNA, and requires a step of chemical modification of the genomic DNA and formation of heteroduplexes with a reference such that "erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA."
>
> The specification teaches methods in which bisulfite treatment is used to convert all unmethylated cytosines to uracil, and thus a resulting erroneous base pair would be produced in the positions at which there were unmethylated cytosines (p. 7, second paragraph). The specification teaches that additional possible reagents for use in the claimed methods are hydrazine and permanganate, but neither of these would result in an erroneous base pair at a position at which a 5-methylcytosine was located in the genomic DNA. There are no working examples that provide a method in which erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA.

> The prior art at the time of the invention does not provide a chemical treatment as required by step (a) of the claim that would result in erroneous base pairs [being] produced in the positions at which a 5-methylcytosine was located in the genomic DNA. Permanganate treatment is a treatment which selectively modifies methylated cytosines, but it does not result in a base change that would cause an erroneous base pairing. Rein et al. (as cited in IDS) provide a review of methods for detecting methylated cytosines and teach that permanganate is a routine method for selectively modifying methylcytosine, but resultant primer extension following the modification would not result in a mismatch but instead in a non-extended sequence (see Table 1; also, p. 2261 and Figure 3).
>
> It is highly unpredictable what chemical modification could result in the chemistry required by claim 6, and claims 9 and 10 which depend from claim 6, as no such chemistries are known. The discovery of such a method would require extensive experimentation and screening to discover such a method.
>
> Thus, in view of these factors, it is concluded that it would require undue experimentation to practice the claimed invention which requires that erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA.

Insofar as the present rejection pertains to claims 9 and 10, the rejection is moot in view of Applicant's amendment of claim 9 to depend from claim 30 and Applicant's cancellation of claim 10. Insofar as the present rejection pertains to claim 6, Applicant respectfully traverses the rejection.

At the outset, Applicant notes that the Patent Office is correct in recognizing that bisulfite treatment results in unmethylated cytosines being converted to uracil while having no such effect on methylated cytosines. However, Applicant disagrees with the Patent Office's assertion that the foregoing fact precludes the possibility that the present method could be used to produce a heteroduplex with an erroneous base pair at a position at which a 5-methylcytosine was located in the sample genomic DNA. This is because the subject heteroduplexes are formed between the sample genomic DNA and reference genomic DNA. As can be appreciated, if the reference genomic

DNA has an unmethylated cytosine at the same position that the sample genomic DNA has a methylated cytosine, bisulfite treatment of both the sample genomic DNA and the reference genomic DNA will result in a conversion of the unmethylated cytosine to uracil in the reference genomic DNA and will have no effect on the methylated cytosine in the sample genomic DNA. The subsequent heteroduplexing of these bisulfite treated DNAs will result in an erroneous base pairing between the methylated cytosine base in the sample genomic DNA and the corresponding uracil base in the reference genomic DNA.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claims 28-29 stand rejected under 35 U.S.C. 102(e) "as being anticipated by Nazarenko et al. (US 6090552)." In view of the cancellation herein of claims 28-29, this rejection is moot and should be withdrawn.

Claims 1-5, 7-8, 11, 18-25, 28 and 29 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Rice et al. (Oncogene (1998) 17, 1807-1812) in view of Gifford (US 5750335)." In support of the rejection, the Patent Office states the following:

> Rice et al. teach a method for identifying 5-methylcytosine positions in a sample genomic DNA, said method comprising the steps of:
>
> (a) chemically treating a sample genomic DNA obtained from at least one cell in such a way that cytosine and 5-methylcytosine react differently and from products with different base pairing behavior (p. 1811, treatment with sodium bisulfite);
>
> (b) amplifying by means of a polymerase reaction a segment of the genomic DNA obtained in step (a) (p. 1811, second column);
>
> (c) performing steps (a) and (b) on a reference genomic DNA (Figure 3, methylation was determined for eight different cell types);
>
> Rice et al. utilize chemical treatment with sodium bisulfite in a method to identify the location of methylated cytosines in genomic DNA. Treatment with bisulfite results in the conversion of

unmethylated cytosine residues to uracil, while methylated cytosine residues remain unchanged. Thus, in a sample with unmethylated sequence (for example the HMEC) there would be no change in sequence, but in a sample with high levels of methylation, after PCR there would be thymines where the methylatd cytosines previously were located. Rice et al. effectively introduce mutations nucleic acid sequences via the treatment with sodium bisulfite. Rice et al. utilize a sequencing method to determine the methylation positions after amplification of the sequences.

With regard to claim 2, in the method taught by Rice et al. positions which are variable between different cell lines are identified (see figure 3).

With regard to claim 3, Rice et al. utilize a bisulfite to treat the genomic DNA.

With regard to claim 4, Rice et al. jointly amplify genomic DNA from several cells, as they necessarily isoloated DNA from more than one cell for each cell line.

With regard to claim 5, Rice et al. separately amplified the DNA from several cell lines, and then treated them all by amplification.

With regard to claim 7, the introduction of erroneous base pairs occurs at positions at which cytosine was located in the genomic DNA.

With regard to claim 8, Rice et al. test unmethylated cell lines (p. 1807, second column; Figure 3).

With regard to claim 18, a nucleotide sequence is considered a "chemical function" that enables a PCR reaction or product to be immobilized on a surface. Therefore, the PCR carried out by Rice et al. necessarily uses a primer that enables the polymerase reaction to be immobilized on a surface. The claim does not actually require an immobilization step.

With regard to claim 25, Rice et al. teach treating and amplifying a reference genomic DNA as in steps (a) and (b) for a number of "reference" sequences.

Rice et al. do not form heteroduplexes from the amplified products for the comparison of a test and reference sample. With regard to claims 28 and 29, Rice et al. teach DNA samples from different cells, some that are methylated and some that are not (as different as possible from one another) and reagents for detecting methylation status in samples. Rice et al. do not teach kits.

Gifford teaches a method for identifying sequence differences between two nucleic acids that comprises the steps of:

(d) forming heteroduplexes from two different nucleic acid samples (Col. 3, lines 40-50);

(e) introducing a detectable label into the heteroduplexes of step (d) by means of a reaction which is specific for non-complementary base pairs (Col. 4, lines 15-20), and

(f) determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label (Col. 4, lines 5-10, 20-25).

Gifford specifically teaches comparing a sample (patient) nucleic acid fragment with a control (normal) nucleic acid fragment (Figure 2).

With regard to claims 4 and 5, Gifford teaches that a test or reference nucleic acid may include monoclonal or polyclonal cell lines (Col. 9, 22-25).

With regard to claim 11, Gifford teach detecting the presence of bound DNA via agarose gel electrophoresis, thus determining the presence of the labeled positions (Col. 13, lines 33-45).

With regard to claim 19, Gifford teaches that the reference or test nucleic acids may be immobilized to a solid surface (Col. 5, lines 1-5; col. 13, lines 1-5). With regard to claim 20, Gifford teaches that "different" reference nucleic acids may be immobilized on a solid surface at different spots, which are considered different reaction vessels (Col. 5, lines 1-5). Further, Gifford teaches the transfer of the amplified products to different vessels (affinity columns or affinity matrix) for purification of the heteroduplexes wherein the products are coupled to a solid support (column 5, lines 47-56).

With regard to claim 21 and 22, Gifford teaches using an enzyme that forms a complex with a non-complementary base pair (Col. 4, lines 10-20), specifically teaching MutS (Col. 7, line 22).

> With regard to claim 23, Gifford teaches a method wherein the enzyme bears a label by which a complex can be displayed (Col. 15, lines 65-67).
>
> With regard to claim 24, Gifford teaches that the label is a fluorescence label (Col. 15, lines 65-66).
>
> With regard to claims 28 and 29, Gifford teaches kits comprising reagents for comparison of a test and reference nucleic acid, which include reagents to detect mismatches, reference nucleic acids, etc.
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methylation detection method taught by Rice et al. so as to have utilized the mutation detection methods taught by Gifford. One would have been motivated to utilize the methods taught by Gifford in order to achieve the express benefits of the methods taught by Gifford which include achieving "rapid and accurate genetic screening and diagnosis by compairing two nucleic acids for differences in their sequences...to locate previously unknown mutations of a nucleotide sequence, and to identify the sequence itself, where the nature and position of the mutation within a region of the genome is unknown, and where the location of the region itself is unknown (Col. 3, lines 25-40)." Furthermore, it would have been prima facie obvious to one of ordinary skill in the art to have included reagents taught by Rice et al. in a kit as taught by Gifford in order to have provided one with a set of reagents for the practice of the method.

Insofar as the present rejection pertains to claims 25, 28 and 29, the rejection is moot in view of Applicant's cancellation herein of these claims. Insofar as the present rejection pertains to claims 1-5, 7-8, 11, 18-24, Applicant respectfully traverses the rejection.

As noted in the present specification, the methylation pattern of a genomic DNA segment provides valuable information regarding gene expression and the like. To determine the methylation pattern of a given segment, one could determine the sequence of the entire segment and then note the presence and location of any methylated cytosines therewithin. However, the present inventor

has noted that such an approach provides more information than is necessary since all that is desired is the methylation pattern of the segment and not the identities of the other bases in the segment. As a result, the aforementioned sequencing technique is ill-suited for determining the methylation pattern of a DNA segment.

As contrasted with the above-described sequencing approach, the present invention permits the methylation pattern of a segment to be readily ascertained without requiring the sequencing of the segment. In reference to claim 1, this is accomplished by (a) chemically treating a sample genomic DNA obtained from at least one cell, cell line, tissue or individual in such a way that cytosine and 5-methylcytosine react differently and form products with different base pairing behavior; (b) amplifying, by means of a polymerase reaction, a segment of the sample genomic DNA obtained in step a); (c) performing steps a) and b) on a reference genomic DNA; (d) forming heteroduplexes from the amplified segments produced in steps b) and c); (e) introducing a detectable label into the heteroduplexes of step d) by means of a reaction, which is specific for non-complementary base pairs; and (f) determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label.

Rice et al. is relied upon by the Patent Office for allegedly teaching above steps (a)-(c). However, Applicant wishes to note that Rice et al. involves the above-described approach of sequencing an entire DNA segment (in this case, a portion of the BRCA1 promoter) in order to ascertain its methylation pattern.

Because Rice et al. does not teach or suggest any of steps (d)-(f) of the method of claim 1, the Patent Office proposes combining Rice et al. with Gifford, Gifford being alleged by the Patent Office to teach steps (d)-(f). However, nothing in Gifford teaches or suggests step (f) of the method

of claim 1. In fact, despite the Patent Office's assertion on page 11, lines 1-2, of the outstanding Office Action that Gifford, at col. 4, lines 5-10 and 20-25, teaches "determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label," no such teaching is found in Gifford. At best, the only statement in Gifford that even remotely touches upon step (f) is a throwaway sentence at the conclusion of the Gifford specification that "[i]t is further anticipated that other kinds of mismatches, such as asymmetric methylation, can be detected with proteins that bind to hemi-methylated nucleic acids, such as methyltransferases, e.g., dam." Such a sentence does not provide the type of guidance or direction necessary to arrive at the claimed invention, but instead, merely represents an invitation to experiment. Moreover, there is clearly no recognition in the foregoing sentence of using heteroduplexes following bisulfite treatment. Consequently, it is only through hindsight reconstruction, using the present specification, that one can piece together the applied references to arrive at the claimed invention. As a result, it can be seen that there is no basis for combining the references in the manner proposed by the Patent Office.

Claims 2-5, 7-8 and 18-24, which depend from claim 1 and recite additional features thereto, are patentable over the applied combination of references for at least the same reasons as claim 1.

Claim 11, which depends from new claim 30 and recites additional features thereto, is patentable over the applied references for at least the same reasons as claim 30. Claim 30 is patentable over the applied combination for references for similar reasons to those given above for claim 1.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claims 12-17 and 26-27 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Rice et al. in view of Gifford as applied to claims 1-5, 7-8, 11, 18-25, 28, and 29 above, and further in view of Koster et al. (US 6428955)." In support of the rejection, the Patent Office states the following:

> The teachings of Rice et al. in view of Gifford are applied herein as applied in the previous rejection. In the method taught by Rice et al. in view of Gifford, sodium bisulfite is used which results in the modification of unmethylated cytosines, and therefore mismatches would occur at positions where cytosine was located in the genomic DNA. Rice et al. in view of Gifford do not teach a method in which the heteroduplex is detected by cleavage of the heteroduplex molecule or in which mass spectrometry is used to analyze the size of the DNA fragments.
>
> With regard to claims 12-14, Koster et al. teach methods for analyzing the size of nucleic acid fragments using mass spectrometry, specifically teaching the use of MALDI-TOF and ESI (Col. 18, line 66-Col. 19, line 11).
>
> With regard to claim 15, which requires that the nucleic acids in step (e) are "adapted" to the performance capacity of the mass spectrometer, Koster et al. teach utilizing a variety of PCR amplification methods to obtain PCR products that they analyze using the mass spec (See examples 14-15, for example). With regard to claim 16, Koster et al. teach utilizing nested PCR to amplify products for detection (Examples 5 and 14, for example), a method which uses primers that are staggered along the DNA with respect to the inner and outer pairs of primers and produce a series of amplification products, at least one of which is within the mass range detectable by means of mass spectrometry. With regard to claim 17, the outer primers of a nested PCR make a larger product with is stepwise larger than the inner PCR product and the outer PCR product is closer to the maximally detectable range of the mass spectrometer.
>
> Claim 26 differs from claim 1 in that in step (b) a primer used in the PCR is fluorescently labeled and provided with a chemical function thereby enabling the immobilization of the ampliicate on the surface, step (e) utilizes a chemical mismatch cleavage methodology, and step (f) utilizes mass spectrometry, wherein in step (g) the

presence or presence and position of the 5-methylcytosine within the genomic DNA is deduced from the length of the cleaved nucleic acids. Claim 27 is similar to claim 26 but requires that a detectable label is introduced into the heteroduplex by an enzymatic reaction which is specific for non-complementary base pairs. This limitation is provided in the methods taught by Rice et al. in view of Gifford.

Koster et al. teaches a method in which a heteroduplex is cleaved by an agent that cleaves the unhybridized portion so that a mismatch results in two products and then detecting these by mass spectrometry to detect the presence of the mismatch (Col. 5, lines 30-40; Col. 23, lines 25-40). Koster et al. further teach primers that are labeled with biotin (a means for immobilizing an amplificate on a surface; col. 35, for example) and primers that are labeled with a radioactive label and oligonucleotides that are fluorescently labeled (Col. 49, for example). In addition, as noted previously in this office action, any nucleic acid sequence itself is considered a "chemical function" that would enable the immobilization of the amplificate on a surface. Claims 26 and 27 never actually require the immobilization of the amplificate on a surface, only that such immobilization is "enabled." Nonetheless, Koster further teach methods in which the sequence to be detected is immobilized to a solid support by means of hybridization (Col. 3, lines 60-67).

It would have been prima facie obvious to one of ordinary skill in the art to have modified the method taught by Rice et al. in view of Gifford et al. so as to have used the amplification and detection methods taught by Koster et al. One would have been motivated to use mass spectrometry as a means for detection of nucleic acid fragments in order to take advantage of the express benefits of such a method as taught by Koster et al., who state "the processes of the invention provide for increased accuracy and reliability of nucleic acid detection by mass spectrometry (Col. 5, lines 62-65). Furthermore, it would have been prima facie obvious to have utilized fluorescently labeled primers in place of the radioactively labeled primers taught by Koster et al. in order to have provided an alternative labeling method that is safer to use as opposed to using radioactivity in the laboratory.

Insofar as the present rejection pertains to claim 17, the rejection is moot in view of Applicant's cancellation herein of claim 17. Insofar as the present rejection pertains to claims 12-16 and 26-27, Applicant respectfully traverses the rejection.

Claims 12-16 depend from claim 30. Claim 30 is patentable over Rice et al. in view of Gifford. Kolster fails to cure the deficiencies of Rice et al. and Gifford. Therefore, claims 12-16 are patentable over the combination of Rice et al., Gifford and Kolster.

Claims 26 and 27 are patentable over the applied combination of references for at least the same types of reasons given above for claim 1 and/or claim 30.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 15, 2004.

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